Mechanical circulatory support challenges in pediatric and (adult) congenital heart disease

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Abstract: PURPOSE OF REVIEW: Increased miniaturization of ventricular assist devices (VADs) and new mechanical support strategies (MCS) has increased the use of MCS in the pediatric and congenital heart disease (CHD) population. This comes with the need for care providers specialized in this field to determine optimal patient and device selection, and to improve outcomes and decrease complication rates for new innovative strategies. A review of the published literature in this field is timely and relevant. RECENT FINDINGS: There has been a rapid evolution of using adult designed continuous flow VADS to support children and adults with CHD (ACHD). Patient selection for patients with CHD is complex because of patient size and anatomical diversity and, therefore, makes decision-making complex and unique when compared to general adult practice. Outcomes for children depend on size and diagnosis with neonates with single ventricle physiology being the highest risk candidates. This also holds true for ACHD, in which VAD outcomes in patients with two ventricle physiology are comparable to non-ACHD patients. SUMMARY: In children, there is an increased use of continuous flow devices and a growing experience with outpatient management. Patients with CHD especially when associated with single ventricle physiologies, remain a challenge when it comes to MCS/VAD placement but successful durable VAD implantation with discharge home has been reported.

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Purpose of review
Increased miniaturization of ventricular assist devices (VADs) and new mechanical support strategies (MCS) has increased the use of MCS in the pediatric and congenital heart disease (CHD) population. This comes with the need for care providers specialized in this field to determine optimal patient and device selection, and to improve outcomes and decrease complication rates for new innovative strategies. A review of the published literature in this field is timely and relevant.

Recent findings
There has been a rapid evolution of using adult designed continuous flow VADS to support children and adults with CHD (ACHD). Patient selection for patients with CHD is complex because of patient size and anatomical diversity and, therefore, makes decision-making complex and unique when compared to general adult practice. Outcomes for children depend on size and diagnosis with neonates with single ventricle physiology being the highest risk candidates. This also holds true for ACHD, in which VAD outcomes in patients with two ventricle physiology are comparable to non-ACHD patients.

Summary
In children, there is an increased use of continuous flow devices and a growing experience with outpatient management. Patients with CHD especially when associated with single ventricle physiologies, remain a challenge when it comes to MCS/VAD placement but successful durable VAD implantation with discharge home has been reported.

Keywords
adult congenital heart disease, congenital heart disease, failing Fontan circulation, failing Glenn circulation, pediatric ventricular assist device

INTRODUCTION

When selecting patients for ventricular assist device (VAD) placement three groups can be distinguished: adult patients with anatomic normal heart which counts for the majority of VAD implants, pediatric patients with anatomic normal hearts, and patients with congenital heart disease (CHD) irrespectively of age. VAD therapy in adults with anatomical normal hearts has developed as a standard treatment option [1]. However, supporting pediatrics and CHD patients is more challenging but a standard arm of the care pathway in end-stage heart failure. The aim of this manuscript is to review current advances in the use of VAD in pediatrics and patients with CHD.

PEDIATRIC VENTRICULAR ASSIST DEVICE SUPPORT IN PATIENTS WITH ANATOMICALLY NORMAL HEARTS

Historically VADs have been used as bridge to transplantation (BTT) or recovery in children. In the last years, there has been an increase in use of mechanical support strategies (MCS) in the pediatric population mainly driven by the development of smaller VADs, namely continuous flow VADs. This is reflected by increasing implant numbers of continuous flow devices especially in patients more than 25 kgs body weight [2,3▪,4,5] (see Fig. 1). With more experience and improved outcomes a change in the paradigm has set in; VADs are no longer viewed as the last treatment option.

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KEY POINTS

- In pediatrics and CHD, there is an increase use of continuous flow devices and a growing experience with outpatient management.
- New technologies (i.e., virtual implantation for VAD placement in complex and small patients) and sharing experiences will assist in determining the optimal device–patient match which will lead to more successful outcomes and ideally an increase in patients discharged home.
- ACHD patients (two ventricle anatomy) provided with a LVAD demonstrated similar survival compared with non-ACHD patients with LVADs.

Device selection

The following considerations are important in determining device selection:

(1) What is the underlying disease? What is causing the failure?
Structural CHD (see section VAD/MCS in patients with CHD) may be leading to failed circulation or is it 'simple' form of myocardial failure.
(2) What is the predicted estimate of time that VAD support will be needed?
In scenarios like myocarditis or postcardiotomy heart failure support using a temporary VAD [6] might be sufficient, whereas in more chronic heart failure prolonged support time needing durable devices might be needed.
(3) Which ventricle(s) requires support?
Does the patient appear to have biventricular failure or is it only one ventricle that needs support is a crucial factor for surgical implantation strategy and postoperative management.
(4) What is the patients weight and body surface area (BSA)?
Size remains an important factor for device selection in children when compared with adults.
(5) Will the patient be able to be discharged or is there something that will prevent discharge?

Using the answers to these questions, the medical team must select the proper device for the patient and avoid patient-device size mismatch.

The current most used (adult designed) devices are HeartMate II/III (Abbott Medical), Heartware Ventricular Assist Device (HVAD) (Medtronic), and in smaller numbers DuraHeart (Terumo Heart) and Incor (Berlin Heart). There have been some devices i.e., DeBakey VAD Child or VentrAssist which are no longer available on the market. Development of pediatric-specific continuous flow VADs, such as the Infant Jarvik, the only remaining VAD in the PUMPKIN trial, was granted conditional approval for Investigational Device Exemption by the US Food and Drug Administration on 30 September 2016 [7].

There is no doubt that the encouraging outcomes in adult continuous flow VAD technology has had a profound impact on its use in children. It is generally accepted in adult-sized adolescents, who need an isolated left ventricular assist device (LVAD), that an implantable continuous flow VAD is the most common type of device used

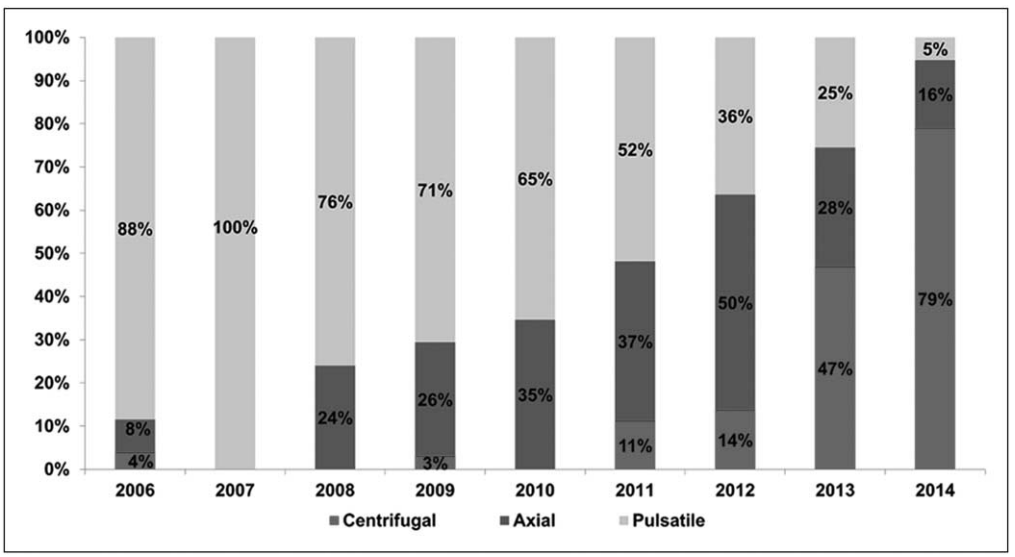

FIGURE 1. There is a distinct increase of continuous flow ventricular assist devices implantations especially in patients more than 25-kgs body weight. Reproduced from [3▪].

[2,3▪,5,8▪▪,9▪,10]. It remains unclear what the size cut off is for the use of these devices in smaller children [11–14].

Each of the current continuous flow devices (Heart Mate II/III, HVAD) in clinical practice have their own approved age and BSA range which varies but is around 1.2 m^2. Continuous flow devices dominate now the field in children above 5 years (56% between 6 and 10 years of age and reaching 90% of older children) and outcomes seem to be non-inferior to pulsatile devices [15]. LVAD placement has been reported down to a BSA of 1 m^2 [8▪▪,16,17▪,18▪,19]. Below this range there are mixed results concerning outcome and adverse even rates [17▪,18▪] [European Registry for Patients with Mechanical Circulatory Support (EUROMACS) paper]. For a BSA below 0.6 m^2 the extracorporeal pulsatile Berlin Heart EXCOR (Berlin Heart) remains the golden standard [20–22]. The new available Berlin Heart EXCOR 15-ml pump chamber seems to close a gap for children less than 0.5 m^2 [23,24]. Overall children weighing less than 10 kg still need to be evaluated very carefully if they have CHD and/or liver dysfunction because their outcomes are inferior [25].

Emerging concepts

Prolonged support

Published survival as BTT or bridge to recovery with pulsatile or continuous flow devices has been reported as high as 97% [4,26] with 6-month survival rates above 80% [5]. The latest Pedimacs reports 6-month mortality rate on device at 16% and a transplantation rate of nearly 50%. So far no pediatric report from the EUROMACS register is published but data from an EUROMACS analysis on intracorporeal continuous flow devices in children refers to an 11% mortality on device at 12 months [28▪▪]. Despite this rather short duration of support it has been shown that that renal function [27▪▪] can improve irrespectively of the device used Berlin heart EXCOR, continuous flow VAD, or temporary device). Although the proportion of patients who develop neurological dysfunction after implantation of pulsatile devices has been documented to be approximately 19–30%, the incidence of cerebral strokes in children supported by continuous flow VADs has not been well explored. A recent report from EUROMACS suggests that it may be as low as 0.1 events per patient-year [28▪▪].

Continuous flow devices have opened the doors to the discharge of pediatric patients on VADs. Whereas some years ago only a few centers reported discharging pediatric patients on continuous flow devices [19], nowadays reported numbers are between 55 [2] and 72% [28▪▪] Most reports suggest that children with a continuous flow VAD can be safely discharged home with device malfunction and arrhythmia being the most common adverse events [29]. Now that children are discharged safely the idea of chronic or prolonged therapy in children is becoming a reality [9▪,30,31]. Current experience with VAD support intended for prolonged therapy (>5 years on device) [9▪] or destination therapy in patients suffering from skeletal myopathies, such as Duchenne disease have been reported [32,33]. However, the percentage of patients categorized as destination therapy remains low (2.1%) [2]. In pediatrics the concept of destination therapy may be different when compared to adult provider beliefs. Char *et al.* suggested that 'providers are reaching a point where they can consider long-term VAD for patients with contraindications to transplant that have the potential to improve, or even can be stabilized long enough for future therapies to emerge [34]. In this sense, destination therapy in children may become more like a long bridge to decision, rather than the adult concept of destination therapy as a true 'destination' [34].

Recovery

It is interesting that although there is huge enthusiasm for home discharge and possibility of prolonged support times there has been little investigation into myocardial recovery in children when compared with adults. This may stem from the lack of reports on the number of children undergoing device for myocardial recovery, the shorter support times compared with adults and the adverse event profiles of some of the available devices [2]. There is currently a lack of standardized guidelines for echocardiographic and hemodynamic criteria for LVAD removal in pediatrics [35] but the pediatric patient population may have great potential for recovery [13]. Extrapolation from adult data may be difficult as it has been shown that myocardial recovery has significant differences when comparing pediatric and adult cardiomyopathy [36,37]. For instance, a comparison of pediatric and adult gene expression changes with VAD support reveals approximately 40% of genes to be oppositely regulated, indicating that the pediatric genetic response is distinct [38].

Intracorporeal biventricular assist device/total artificial heart

The majority of implants in children are only for isolated left ventricular (LV) support. However, there is a certain percentage of patients who require biventricular support with the most recent Pedimacs

report suggesting 15% of patients were supported with a biventricular assist device (BiVAD) and 2% with a total artificial heart (TAH) [2]. Results for biventricular support have been reported to be inferior to LVAD only [39]. Although the Berlin Heart EXCOR remains the 'golden standard' for biventricular support in children some centers have published case series using two continuous flow VADs in pediatrics with successful BTT with BSA as low as 0.6 m^2 [40,12,41,42]. There are even reports of using two continuous flow VADs in a patient with Fontan circulation with subsequent discharge home [43].

Morales *et al.* [44▪] published the global experience using Syncardia TAH in 43 patients at least 21 years with positive outcome of 70% (60 days), 63% (90 days), and 58% (120 days). Owing to the large footprint of the 70-ml TAH, a 50 ml has now become available for patients with BSA as low as 1.2 m^2. TAH placement using 'virtual implantation' may help assess device fit and has evolved as an accepted preoperative planning tool [45].

VENTRICULAR ASSIST DEVICE/ MECHANICAL SUPPORT STRATEGIES PATIENTS WITH CONGENITAL HEART DISEASE

With the increase in the number of survivors following neonatal and infant palliative heart surgery there have been an increase in the number of patients developing end-stage failure. It is estimated that 10–20% of patients with CHD will require heart transplantation at some point of their life. Patients with CHD and end-stage heart failure that need VAD support have worse outcomes when compared with children with cardiomyopathy [25]. Patients, irrespectively of age, with CHD represent a unique and difficult patient population to support with VAD/ MCS. Although some of these patients might need postcardiotomy circulatory support until myocardial recovery others may require a durable VAD because of the absence of myocardial recovery. Short-term extracorporeal devices like extracorporeal membrane oxygenation or short-term continuous flow VADs are used more often in complex CHD patients than durable VADs [46]. However, when durable VAD support using the Berlin Heart EXCOR is necessary it has been shown to be more successful in children greater than 1 year of age when compared with the neonatal and infant cohort [47▪▪]. Recently, Morales *et al.* reported the results of the Berlin Heart EXCOR in patients with CHD [47▪▪]. One third of all EXCOR patients had CHD and of these 30% had a univentricular physiology [47▪▪]. The report showed that durable VADs should be used very cautiously in children suffering from complex CHD below 1 year of age, especially patients on previous extracorporeal membrane oxygenation and those who had prior cardiac surgery [47▪▪].

Mechanical support strategies in single ventricle physiology

Trials investigating the use of MCS in patients with single ventricle do not exist. Information largely stems from small case series or single case reports. These reports have revealed high mortality rates (two or three patients dying prior to discharge [48▪▪]) and adverse events, compared to with two ventricular physiology [49]. There are multiple reasons for these findings, it may be that the mechanism of failure at different stages of surgical palliation is not amendable to VAD support.

There is a variety of anatomical variations that result in single ventricle physiology. In affected newborns with a lack of pulmonary blood flow the first step is to establish sufficient flow to the pulmonary arteries (natural via patent ductus arteriosus or surgical creation of a shunt) and balance this with maintenance of the cardiac output. In the second stage, around 4–6 months of age, the creation of a superior cavopulmonary anastomosis ensures blood flow to the pulmonary arteries (Glenn operation) and in the third step (Fontan operation), done around 2–4 years of age, the inferior vena cava is anastomosed to the pulmonary artery (Fontan circulation). Heart failure or circulatory failure can occur during any of these three stages and remains a challenge to manage. Feasibility of VAD support for Glenn circulation has been proven to be [50] associated with persistent cyanosis resulting in exercise intolerance, extensive collateralization and suboptimal outcome [49,51]. Adachi *et al.* [52] suggested to avoid long-standing cyanosis, completion of the Fontan circulation should occur at the time of VAD implantation when implanted in a Glenn circulation.

Most often Fontan failure presents as a failing Fontan circulation rather than isolated myocardial dysfunction. The pathophysiology of failure tends to be multifactorial reason [53,54]: with diastolic dysfunction commonly observed; further, increased pulmonary vascular resistance inhibits the venous return and results, therefore, in a reduced systemic preload, cardiac output, and the development of collateral vessels in various locations. When the systolic function is characteristically preserved currently available MCS devices are unable to support the patient because they are designed to provide systemic circulatory support, not cardiopulmonary support. Consequently, hemodynamic support for

failing Fontan circulation that is not solely because of myocardial dysfunction is not yet well defined. Various concepts for a pump in the cavopulmonary position are under current research. Whereas some of these concepts are specifically designed for support of the total cavopulmonary connection t [55,56], others have reported the use of currently available VADs [57–60]. Most of the proposed designs do not constitute an option for implantable long-term destination therapy for Fontan patients because of their design or their size. Most notably, these patients have a documented increased risk of hepatic [61], neurologic, and respiratory complications associated with the use of MCS/VAD [62]. Despite these potential adverse events, durable VAD implantation in Fontan patients is increasing with some patients being discharge home [43,63–65].

Population of adults with congenital heart disease with two ventricle anatomy/ physiology

Owing to improved surgical techniques and perioperative treatment options deaths and hospitalizations in CHD have shifted from infancy to adulthood. The population of adults with CHD (ACHD) currently exceeds the number of children with CHD in many western countries and the use of durable VAD utilization in ACHD are becoming more frequent [66]. In ACHD patients suffering from complex CHD heart failure remains the leading causes for mortality and accounts for 20% of hospital admissions [67]. Adequate risk stratification focusing on mortality and morbidity in this population, whose heterogeneous pathophysiology differs from that of the general heart failure population, are still missing [68]. This explains in parts why ACHD patients are less frequent implanted with VADs compared to acquired disease patients [69,70] and represent a small portion (<1%) of the total Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) population [61]. One may link this to a higher published adverse event and an increased mortality rate [61] which is only partial true. The higher mortality rate is exclusively attributable to ACHD patients on BiVAD/TAH support. ACHD and non-ACHD patients with LVADs demonstrated similar survival regardless of cardiac anatomy [61]. The present data from Vanderplyum *et al.* also suggest a possible role for increased LVAD use as destination therapy in this population patients as the median age of ACHD patients provided with a VAD is significant lower (16%) compared with non-ACHD patients [61].

In two ventricular circulations one has to distinguish if there is a systemic morphologic LV or systemic morphologic right ventricle (RV). A systemic morphologic RV is present in patients with transposition of great arteries (TGA) with ventricular-atrial and ventricular-arterial discordance (congenital corrected TGA, congenital corrected transposition of the great arteries) or surgical corrected dextrp Transposition of the great arteries (ventricular-arterial discordance) using atrial switch procedure (Senning or Mustard operation). Nowadays the arterial switch operation (ASO), which fully restores the correct anatomical structure of the heart, has become the primary method of choice for surgical correction. Before the ASO was applied the ASO (Senning or Mustard operation) was done. Many patients who have undergone ASO may suffer from end-stage heart failure of the systemic RV and will benefit from VAD support [61,66,71]. Limited data und numbers, however, make standardized approaches difficult; i.e., device selection, implanting location of the inflow cannula into systemic morphologic RVs [61,72–75].

ACHD patients differed most notably from non-ACHD patients in expected ways, including younger age, greater allosensitization, more RV dysfunction, and unfavorable mediastinal anatomy at time of device implantation. Most ACHD had multiple previous cardiac surgery and interventions, which adds to the complexity of the surgical procedure at the time of VAD placement. Additionally, aortopulmonary collaterals increase the bleeding risk which makes the operating field hard to visualize sufficiently. Therefore, preoperative assessment including sufficient imaging remains a crucial part of the success. As recommended by the 2010 International Society for Heart and Lung Transplantation guidelines all patients with CHD should have recent imaging to access for the presence of shunts or collateral vessels (Class 1, C) [1]. In patients with complex CHD, atypical situs, or residual intraventricular shunts who are not candidates for LV support should be considered for a TAH [1].

CONCLUSION

Availability and outcome of continuous flow devices in pediatrics has changed the field. The era of pediatric continuous flow VAD support has begun. [...] The popularization of continuous flow VADs represents a paradigm change in the field'[9▪]. Patients with CHD especially those with single ventricle physiology remains a challenging population. In ACHD, LVAD patients with two ventricle physiology outcomes are comparable to non-ACHD

patients and an increasing permanent support can be expected.

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Conflicts of interest

There are no conflicts of interest.

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